Re: Second Cancers After Adjuvant Tamoxifen Therapy for Breast Cancer

Curtis et al. state "... we found little evidence that tamoxifen treatment increases the incidence of colorectal or stomach cancer significantly, as reported by Rutqvist et al." (*1*). In fact, the data of Curtis et al. offer little evidence to controvert the findings of Rutqvist and colleagues from the Stockholm Breast Cancer Study Group (*2*).

The data from the Surveillance, Epidemiology, and End Results (SEER) Program[1] that Curtis et al. present may be biased toward the null value by the failure to consider induction time. This failure is equivalent to assuming that the latent period for tamoxifen-induced gastrointestinal cancers is zero. This assumption results in the dilution of data on truly exposed patients who have had sufficient time to develop the disease under study with data on patients who would be more correctly categorized as unexposed (*3*). Such dilution is especially important given the short follow-up of the SEER study—the mean duration of follow-up for the tamoxifen-treated group was only 2.8 years (14 358 patients; 39 736 person-years at risk). In contrast, the median follow-up for the patients reported by the Stockholm Breast Cancer Study Group was 8-9 years.

In spite of this bias in follow-up time, the 95% confidence intervals for the odds ratios for stomach and colorectal cancers reported by Curtis et al. overlap those of the Stockholm Breast Cancer Study Group and remain consistent with a 30%-49% increase in risk of colorectal cancer and as much as a 103% increase in risk of stomach cancer. Clearly, further data obtained from patients exposed to tamoxifen for longer periods will be required before we can dismiss the possibility of an increase in the risk of gastrointestinal cancers due to this drug.

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References

(*1*) Curtis RE, Boice JD Jr, Shriner DA, Hankey BF, Fraumeni JF Jr. Second cancers after

adjuvant tamoxifen therapy for breast cancer. J Natl Cancer Inst 1996;88:832-4.
(*2*) Rutqvist LE, Johansson H, Signomklao T, Johansson U, Fornander T, Wilking N. Adjuvant tamoxifen therapy for early stage breast cancer and second primary malignancies. Stockholm Breast Cancer Study Group [*see* comment citations in Medline]. J Natl Cancer Inst 1995;87:645-51.
(*3*) Rothman KJ. Types of epidemiologic study. Modern epidemiology. Boston: Little, Brown, 1986:58-9.

Notes

[1]Editor's note: SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

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Curtis et al. (*1*) described the incidence of second cancers among 14 358 breast cancer patients reported to the Surveillance, Epidemiology, and End Results (SEER) Program who received adjuvant tamoxifen therapy. They found a significant excess of endometrial cancer in accordance with several previous reports but no excess of stomach and colon cancers as reported from three Scandinavian adjuvant tamoxifen trials.

Although the SEER data may provide relevant information on the effects of short-term adjuvant tamoxifen therapy, they appear to be of little value for judging the long-term effects of high cumulative doses of tamoxifen (e.g., the cumulative dose resulting from a 20-mg-daily schedule for 5 years, which now has become the standard treatment for most breast cancer patients).

In many studies of second cancer incidence after adjuvant tamoxifen therapy, there appears to be a direct relationship between the cumulative dose of tamoxifen and the relative risk of endometrial cancer. In the Stockholm trial, with an average cumulative dose of 42 g, the relative risk was about 6 (*2*). This excess was similar to that observed in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial with a protocol cumulative dose of 37 g (*3*). In trials using, cumulative protocol doses of 11 g, the excess of endometrial cancer corresponded to a relative risk on the order of 2-3 (*4*,*5*).

In the study by Curtis et al. (*1*), there was no information on the tamoxifen doses actually received by the patients. However, the published figures indicate that the average cumulative dose was low. The ratio between the observed and the expected numbers of endometrial cancer cases among the tamoxifen-treated patients was 2.03. The corresponding ratio for those patients not treated with tamoxifen was 1.23. These figures suggest a relative risk of endometrial cancer of less than 2.0 associated with the use of tamoxifen in the SEER material. Given the mentioned results from previous trials, such a low figure is what one would expect with an average cumulative dose of less than 10 g. This is perhaps not surprising in view of the fact that the patients were treated during the period 1980 through 1992, when schedules of only 1 or 2 years of tamoxifen were common. Thus, the SEER database does not appear to include many patients treated with tamoxifen doses that are relevant to current medical practice. In addition, as stated by the authors, few patients were followed for more than 10 years.

The mechanisms involved in tamoxifen carcinogenesis are not fully understood. It would appear that tamoxifen may have both tumor-initiating and tumor-promoting properties (*2*,*6*-*9*). Part of the promoting effect may be related to the estrogenic agonistic effects of tamoxifen. Such estrogenic effects may explain the early excess of endometrial cancer associated with tamoxifen therapy that has been observed in many studies. In contrast, tumor-initiating effects, for instance, related to the documented DNA-adduct-forming ability of tamoxifen, cannot be expected to show up until after several years of follow-up. Therefore, I agree with Curtis et al. that further studies of breast cancer survivors are needed to monitor site-specific risks of cancer over time in relation to duration and dose of tamoxifen.

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References

(*1*) Curtis RE, Boice JD Jr, Shrines DA, Hankey BF, Fraumeni JF Jr. Second cancers after adjuvant tamoxifen therapy for breast cancer. J Natl Cancer Inst 1996;88:832-4.
(*2*) Rutqvist LE, Johansson H, Signomklao T, Johansson U, Fornander T, Wilking N. Adjuvant tamoxifen therapy for early stage breast cancer and second primary malignancies. Stockholm Breast Cancer Study Group [*see* comment citations in Medline]. J Natl Cancer Inst 1995;87:645-51.
(*3*) Fisher B, Costantino JP, Redmond CK, Fisher ER, Wickerham DL, Cronin WM. Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 [prior annotation incorrect] [*see* comment citations in Medline]. J Natl Cancer Inst 1994;86:527-37.
(*4*) Andersson M, Storm HH, Mouridsen HT. Incidence of new primary cancers after adjuvant tamoxifen therapy and radiotherapy for early breast cancer. J Natl Cancer Inst 1991; 83:1013-7.
(*5*) Ryden S, Ferno M, Moller T, Aspegren K, Bergljung L, Killander D, et al. Long-term effects of adjuvant tamoxifen and/or radiotherapy. The South Sweden Breast Cancer Trial. Acta Oncol 1992;31:271-4.
(*6*) Han XL, Liehr JG. Induction of covalent DNA adducts in rodents by tamoxifen. Cancer Res 1992;52:1360-3.
(*7*) White IN, de Matteis F, Davies A, Smith LL, Crofton-Sleigh C, Venitt S, et al. Genotoxic potential of tamoxifen and analogues in female Fischer F344/n rats, DBA/2 and C57BL/6 mice and in human MCL-5 cells. Carcinogenesis 1992;13:2197-203.
(*8*) Greaves P, Goonetilleke R, Nunn G, Topham J, Orton T. Two-year carcinogenicity study of tamoxifen in Alderley Park Wistar-derived rats. Cancer Res 1993;53:3914-24.
(*9*) Metzler M, Schiffmann D. Structural requirements for the in vitro transformation of Syrian hamster embryo cells by stilbene estrogens and triphenylethylene-type antiestrogens. Am J Clin Oncol 1991;14:530-5.

Note

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Response

Dr. Atkins indicates that the risks we presented for gastrointestinal cancer following tamoxifen treatment of breast cancer are biased toward the null because we failed to consider induction time. Moreover, he maintains that our ability to detect increased risks among long-term survivors is limited because of the short follow-up in the Surveillance, Epidemiology, and End Results (SEER) Program database. The possibility of a minimum latency period for second cancers was explored in Table 2 of our brief communication (*1*).

Although the mean follow-up was 2.8 years, the number of tamoxifen-treated patients who survived 5 or more years (n = 2293) was close to the total number of tamoxifen-treated patients in the three Scandinavian trials (n = 2475) (*2*). Our results showed only a slight nonsignificant increase in risk of gastrointestinal cancer in the interval of 5 years or more among those treated with tamoxifen (observed/expected [O/E] = 1.29; 95% confidence interval [CI] = 0.83-1.92). However, we acknowledged that SEER currently has limited ability to evaluate risk among 10-year survivors. In response to Dr. Atkins' concern, we have analyzed separately 818 tamoxifen-treated patients in SEER who survived at least 7 years; no significant excess of gastrointestinal cancer was found (observed = 9; O/E = 1.43; 95% CI = 0.65-2.71), although the risk of uterine corpus cancer remained elevated. In Scandinavia, Rutqvist et al. (*2*) reported a 1.9-fold increase in risk of gastrointestinal cancer associated with tamoxifen therapy (95% CI = 1.2-2.9), but they provided no information on risk among survivors of 5 or more or of 10 or more years.

Dr. Rutqvist notes that the current SEER data may be limited in judging the long-term effects of high cumulative doses of tamoxifen, especially the current tamoxifen schedule of 20 mg/day for 5 years. Actually, few studies have been able to evaluate risk of second cancers among long-term tamoxifen users, since 5-year regimens have only recently been widely used (*3*,*4*). In the Scandinavian study (*2*), more than 80% of the 2475 patients had 1-2 years of tamoxifen therapy, with maximum doses ranging from 11 to 29 g (45% had 30 mg/day for 1 year; 39% had 40 mg/day for 2 years; 16% had 40 mg/day for 5 years). Thus, the tamoxifen-related excesses of endometrial and gastrointestinal cancers observed in the Scandinavian trials appear to be based primarily on therapy given for fewer than 2 years. Further data on long-term tamoxifen use are provided by the large National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial, with 2639 patients receiving 20 mg/day for 5 or more years (*5*). The risks of endometrial cancer in the randomized, tamoxifen-treated group were 7.5 compared with the placebo group, 2.2 compared with population-based incidence rates, and 2.3 compared with data from the NSABP B-06 trial. The last two estimates resemble the twofold risk that we observed in the SEER database. The NSABP B-06 trial yielded no excess of colorectal or stomach cancer. Furthermore, two case-control studies (*6*,*7*) have found a significant trend of increasing risk of endometrial cancer with increasing duration of tamoxifen use, with threefold risks noted for users of 5 or more years.

Although information on duration of tamoxifen therapy is not available in SEER, it is possible to evaluate a subset of our cohort treated during a period when longer term tamoxifen therapy was gradually introduced (Table 1). The risks of cancers of the gastrointestinal tract and uterine corpus among patients receiving tamoxifen in the period 1985-1992 were similar to the risks among those treated during 1980-1984, whereas the risk of contralateral breast cancer fell to levels comparable to those of the general population. Estimation of risks of second cancers occurring beyond 5 years in the 1985-1992 period was limited by small numbers of person-years at risk.

Dr. Rutqvist suggests that the relative risk of uterine corpus cancer after breast cancer in our study is likely to be lower than the 2.03 risk observed in the tamoxifen group, since a 1.23 risk was seen in the no/unknown tamoxifen group. We did note in our brief communication (*1*) that at least part of the excess risk observed in the no/unknown tamoxifen group was related to tamoxifen therapy not reported to the SEER Program. Comparing the observed uterine corpus cancers incidence rates among tamoxifen-treated patients to that expected from the SEER population (O/E = 2.03) provides the most appropriate estimate, since breast cancer patients treated before the introduction of tamoxifen had a risk of uterine cancer similar to that of the general population.

In commenting on possible carcinogenic mechanisms, Dr. Rutqvist suggests that tamoxifen may have both tumor-promoting and tumor-initiating effects related to its capacity to form DNA adducts in laboratory animals. Although there is some evidence that humans may be less efficient in metabolizing the active compound α-hydroxytamoxifen (*8-10*), additional studies are needed on the possible genotoxic effects of tamoxifen. Most importantly, as noted by Drs. Atkins and Rutqvist, the risk of second cancers following tamoxifen therapy will be clarified only when large numbers of breast cancer patients are followed for long periods with detailed data on dose, duration of exposure, and potential confounders.

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Table 1. Risk of selected second primary cancers among women treated with tamoxifen for breast cancer, aged 50 or more years, with localized or regional stage disease, who did not receive chemotherapy, by site and calendar year of initial breast cancer diagnosis*

	Calendar year of initial breast cancer diagnosis					
	1980-1984			1985-1992		
Second site	O	O/E	95% CI	O	O/E	95% CI
All digestive cancers	30	0.99	0.67-1.41	123	1.03	0.85-1.23
Stomach	3	1.18	0.24-3.45	12	1.24	0.64-2.17
Colon, rectum	20	0.97	0.59-1.50	86	1.05	0.84-1.30
Breast (contralateral)	44	1.57	1.14-2.11	133	1.02	0.85-1.21
Uterine corpus	16	2.44	1.39-3.96	57	1.94	1.47-2.51
No. of patients	1277			13 081		
Person-years at risk	7101			32 628		

*O = observed number of second cancers; O/E = observed-to-expected ratio; CI = confidence interval.

References

(*1*) Curtis RE, Boice JD Jr, Shriner DA, Hankey BF, Fraumeni JF Jr. Second cancers after adjuvant tamoxifen therapy for breast cancer. J Natl Cancer Inst 1996;88:832-4.

(*2*) Rutqvist LE, Johansson H, Signomklao T, Johansson U, Fornander T, Wilking N. Adjuvant tamoxifen therapy for early stage breast cancer and second primary malignancies. Stockholm Breast Cancer Study Group [*see* comment citations in Medline]. J Natl Cancer Inst 1995;87:645-51.

(*3*) Fisher B, Costantino J, Redmond C, Poisson R, Bowman D, Couture J, et al. A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumors [prior annotation incorrect]. N Engl J Med 1989;320:479-84.

(*4*) Adjuvant tamoxifen in the management of operable breast cancer: the Scottish trial. Report from the Breast Cancer Trials Committee, Scottish Cancer Trials Office (MRC), Edinburgh. Lancet 1987;2:171-5.

(*5*) Fisher B, Costantino JP, Redmond CK, Fisher ER, Wickerham DL, Cronin WM. Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 [prior annotation incorrect] [*see* comment citations in Medline]. J Natl Cancer Inst 1994;86:527-37.

(*6*) van Leeuwen FE, Benraadt J, Coebergh JW, Kiemeney LA, Gimbrere CH, Otter R, et al. Risk of endometrial cancer after tamoxifen treatment of breast cancer [*see* comment citations in Medline]. Lancet 1994;343:448-52.

(*7*) Sasco AJ, Chaplain G, Amoros E, Saez S. Endometrial cancer following breast cancer: effect of tamoxifen and castration by radiotherapy. Epidemiology 1996;7:9-13.

(*8*) Martin EA, Rich KJ, White IN, Woods KL, Powles TJ, Smith LL. ^{32}P-postlabelled DNA adducts in liver obtained from women treated with tamoxifen. Carcinogenesis 1995;16:1651-4.

(*9*) Carmichael PL, Ugwumadu AH, Neven P, Hewer AJ, Poon GK, Phillips DH. Lack of genotoxicity of tamoxifen in human endometrium. Cancer Res 1996;56:1475-9.

(*10*) Phillips DH, Hewer A, Grover PL, Poon GK, Carmichael PL. Tamoxifen does not form detectable DNA adducts in white blood cells of breast cancer patients. Carcinogenesis 1996;17:1149-52.

Notes

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